(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 August 2001 (23.08.2001)

PCT

(10) International Publication Number
WO 01/60823 A1

(51) International Patent Classification[7]: C07D 471/08, A61K 31/4995, A61P 25/04

(21) International Application Number: PCT/EP01/01541

(22) International Filing Date: 13 February 2001 (13.02.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI2000A000293 18 February 2000 (18.02.2000) IT

(71) Applicant *(for all designated States except US)*: **IL CENTRO CONSORTILE RICERCHE NEUROPSICOFARMACOLOGICHE A R.L.** [IT/IT]; Via Palabanda, 9, I-09125 Cagliari (IT).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **CIGNARELLA, Giorgio** [IT/IT]; Via Vanvitelli 49, I-20129 Milano (IT). **PINNA, Gérard, Aimé** [IT/IT]; Via Prunizzedda 88B, I-07100 Sassari (IT).

(74) Agents: **MINOJA, Fabrizio** et al.; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I-20122 Milan (IT).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

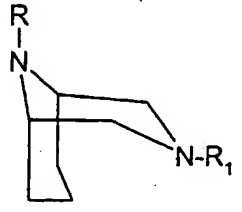
Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/60823 A1

(54) Title: 3,9-DIAZABICYCLO[3.3.1]NONANE DERIVATIVES WITH ANALGESIC ACTIVITY

(57) Abstract: Compounds of formula (I) wherein R and R_1, which are different from each other, are a straight or branched C_2-C_8 acyl group, have analgesic activity.



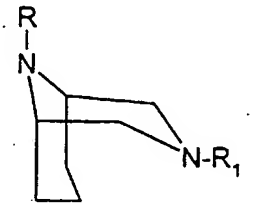
(I)

20

3,9-DIAZABICYCLO[3.3.1]NONANE DERIVATIVES WITH ANALGESIC ACTIVITY

The present invention relates to 3,9-diazabicyclo[3.3.1]nonane derivatives, the use thereof for the preparation of medicaments with central analgesic activity and pharmaceutical compositions containing them.

In particular, the invention relates to compounds of general formula (I)



(I)

wherein

R and R_1, which are different from each other, are a straight or branched C_2-C_8 acyl group;

a group of formula

$$-CH_2-CH=C(-R_2)-B \quad \text{or} \quad -CH_2-CH_2-CH(-R_2)-B$$

wherein:

B is a C_6-C_{10} aryl group, optionally substituted at the ortho-, meta- or para- positions with one or more substituents, which are the same or different, selected from the group consisting of C_1-C_3 alkoxy, C_1-C_2 halo alkyl, C_1-C_3 alkyl, halogens, carboxy, cyano, nitro, $CONHR_3$; a C_5-C_7 cycloalkyl group, a 5 or 6 membered heterocyclic aromatic group, optionally benzofused, having at least one heteroatom selected from nitrogen, oxygen, sulfur; said heterocyclic group optionally having one or more substituents as described above for the aryl group;

R_2 is hydrogen, C_1-C_4 alkyl, C_5-C_7 cycloalkyl or a phenyl group

optionally substituted as indicated above,

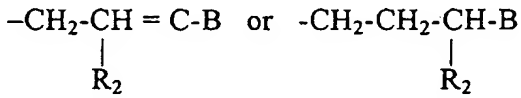
and the pharmaceutically acceptable salts thereof.

Examples of C_1-C_8 acyl groups are acetyl, propionyl, isopropionyl, butyryl, isobutiryl, valeryl, isovaleryl, pivaloyl, caproyl.

Examples of heterocyclic groups are pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyridine, pyrimidine, pyridazine, pyrazine, benzothienyl.

Examples of pharmaceutically acceptable salts are those with halohydric acids, such as hydrochloric acid, hydrobromic acid; mineral acids, such as sulfuric and phosphoric acids; organic acids, such as acetic, propionic, succinic, glutaric, benzoic, salicylic acids. Any carboxylic groups can be in the salified form with alkali or alkaline-earth metal bases, such as sodium, potassium, calcium, magnesium; bases of non toxic metals; non toxic organic amines.

Preferred are compounds of formula (I) wherein R or R_1 are an acyl group as defined above or a group of formula



and B is a phenyl group, optionally substituted, as defined above, a naphthyl or a heterocyclic group.

Also preferred are compounds of formula (I) wherein R_1 is an acyl group as defined above and R is the group of formula 

3,8-Diazabicyclo[3.2.1.]octane derivatives with analgesic activity are disclosed in EP 0 746 560.

It has now been found that the compounds of formula (I) have central analgesic activity comparable to that of morphine and higher than that of 3,8-diazabicyclo[3.2.1.]octane, are "substantially free" from withdrawal

symptoms and less liable than morphine to induce tolerance or physical dependence after chronic treatment.

"Substantially free" herein means an activity 3 to 20 times lower than that of morphine in the mouse jumping test, after chronic administration three times a day for 7 consecutive days of analgesically equipotent dosages.

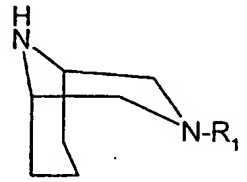
The present invention also relates to the compounds of general formula (I) as agents with central analgesic activity.

A further object of the present invention are the processes for the preparation of said compounds.

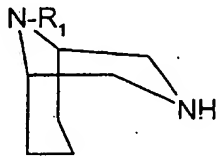
Still a further object of the present invention is the use of the compounds of formula (I) for the preparation of a medicament useful to induce analgesia on central nervous system in a mammal, particularly in humans, requiring such treatment.

Still a further object of the invention are pharmaceutical compositions containing a therapeutically effective amount of at least one compound of formula (I) in mixture with conventional carriers and excipients.

The compounds of the invention can be prepared by reaction of intermediates of formula (IIa) or (IIb)



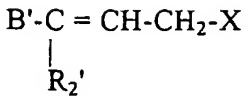
IIa



IIb

wherein R' is a straight or branched C_2-C_8 acyl group

with a compound of formula



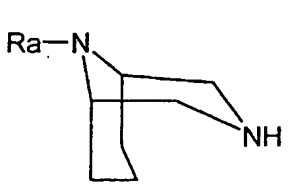
(III)

wherein R_2' and B' have the same meanings as R_2 and B or are groups which can be transformed into R_2 and B, and X is a leaving group, for example a halogen atom, mesyl, tosyl and the like.

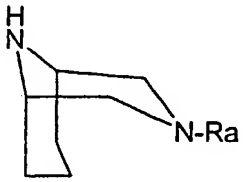
The reactions described above are carried out according to conventional techniques known to those skilled in the art. Reagents are usually present in stoichiometric or slightly different ratios, depending on the reactivity of the specific reagent.

The acylation of the nitrogen at 3 or at 9 is usually carried out with acid chlorides in an inert reaction medium, such as an open or closed chain ether, a ketone, an optionally halogenated hydrocarbon, preferably in the presence of a proton-acceptor, such as a tertiary amine. Alternatively, the acylating agent can be a carboxylic acid anhydride.

The intermediates of formulae (IIa) and (IIb) can be obtained by acylation, according to conventional methods, of a compound of formula (IVa) or (IVb)



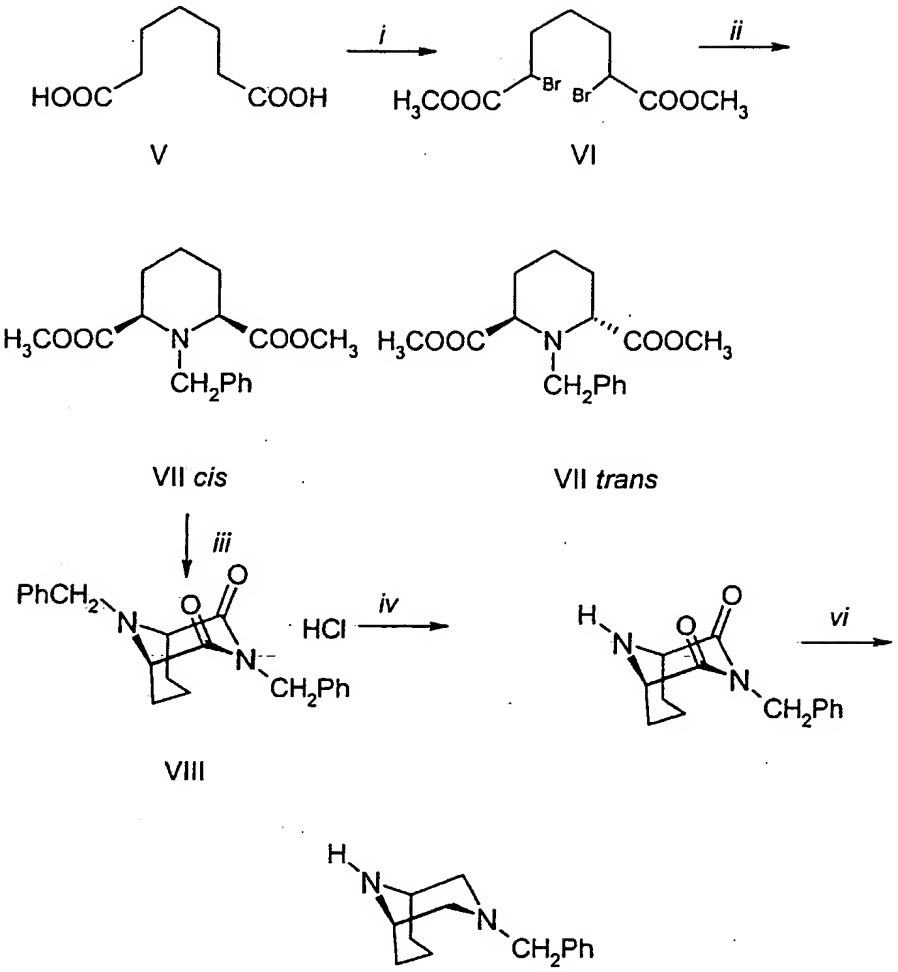
IVa



IVb

wherein Ra is an amino-protecting group, and subsequent removal of the protective group. Compound of formula (IVa) in which Ra is benzyl is known from Gazzetta Chimica Italiana, 1963, 226-227, and can be prepared according to the following scheme 1

Scheme 1



Meso-dimethyl-α,α-dibromopimelate (VI) obtained by bromination of pimelic acid (V), is condensed with benzylamine in benzene under reflux to give N-benzyl-2,6-dicarbomethoxy-piperidine (VII) as cis and trans isomeric mixture, which is reacted with benzylamine in xylene under reflux for 18 hours and then, after evaporation of the solvent, for a further 4 hours a 160-170°C

The resulting compound (VIII) is recovered as hydrochloride from the

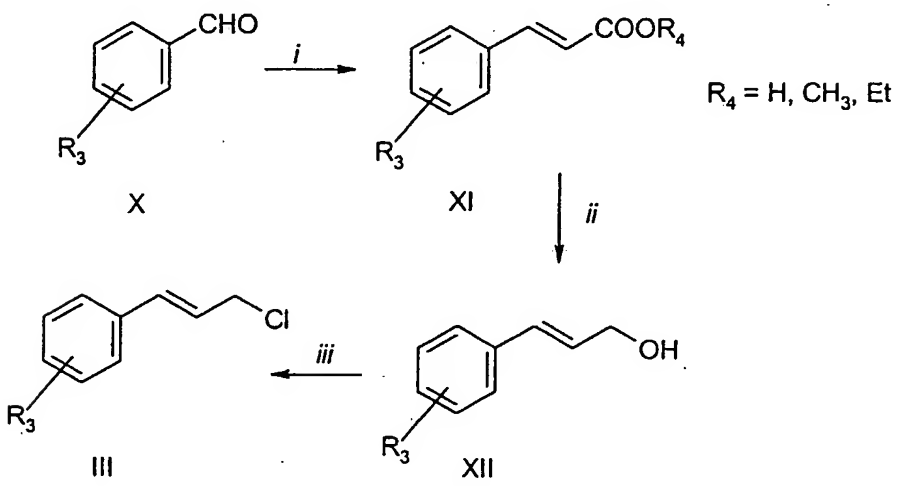
reaction product by dissolution in ethanol and precipitation with HCl, then is hydrogenolysed to give the compound (IX) which is reduced with metal hydrides such as $LiAlH_4$, to yield compound (IVa).

Compounds (IVb) can be obtained from compounds (IVa) through thermal rearrangement, analogously to what published for the homologous diazabicyclooctanes (Tetrahedron, 1963, 9, 143-148).

Intermediates of formula (III) are known or can be prepared with known methods, for example by reducing suitable arylacryl acids or esters thereof with metal hydrides and subsequently transforming the resulting alcohol into halide, with conventional methods, according to Scheme 2 reported in the following, concerning compounds (III) in which B is optionally substituted phenyl and R_2 is hydrogen. Other compounds of formula (III) can be obtained with similar methods.

In Scheme, R_3 represents the substituents listed for the aryl group R_2.

Scheme 2



Compounds (I) and the salts thereof with pharmaceutically acceptable acids can be advantageously used as active principles in medicaments having central analgesic activity, as well as poor liability to induce tolerance and withdrawal symptoms which are the most serious restrictions to the use of

morphine.

For the envisaged therapeutical uses, compounds (I) or the salts thereof will be formulated in a therapeutically effective amount in suitable pharmaceutical formulations according to conventional techniques and excipients, such as those described in "Remington's Pharmaceutical Sciences Handbook" XVII Ed. Mack Pub., N.Y., USA.

Examples of pharmaceutical compositions are tablets, capsules, granulates, powders soluble, drops, elixirs, syrups, injectable forms, suppositories.

The dosages and posology will be defined by the physician depending on the severity of the disease, the conditions of the patient and any possible interactions with other medicaments.

The following examples further illustrate the invention.

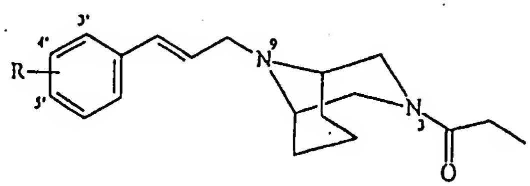
Preparation 1

3-Propionyl-3,9-diazabicyclo[3.3.1]nonane.

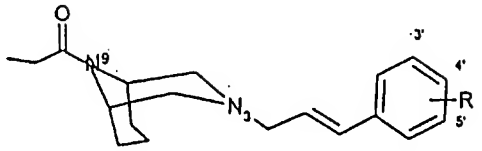
9-Propionyl-3,9-diazabicyclo[3.3.1.]nonane (IVa) (0.83 g, 4.56 mmol) obtained according to Gazzetta Chimica Italiana 1963, 226-227 was heated at 150°C for 2 hours. The crude product was chromatographed (silica gel) eluting with $CHCl_3$-CH_3OH/8:2.

The title product was recovered from the fraction with R_f 0.29 as oil, b.p. 125-130°C/0.4 mmHg. IR (film, cm^{-1}) ν: 1630 (C=O), 2920 (NH); ^{1}H-NMR ($CDCl_3$) δH: 1.16 (t, 3H), 1.50-1.70 (m, 2H), 1.80-2.20 (m, 4H), 2.35 (q, 2H), 3.15 (dd, 1H), 3.33 (br s, 2H), 3.65 (dd, 1H), 3.88 (d, 1H), 4.79 (br s, 1H exch. with D_2O). ^{13}C-NMR ($CDCl_3$) δc: 9.05 (CH3), 18.24, 26.64, 29.48, 29.49, 45.08 and 49.22 (CH2x6), 46.53 and 46.61 (CHx2), 172.58 (C=O) from DEFT (135°C) and HETCOR.

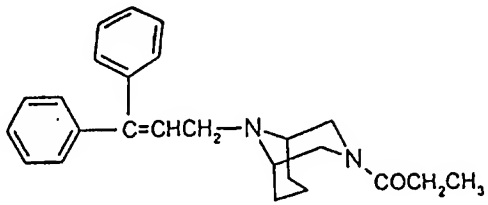
EXAMPLES 1-16



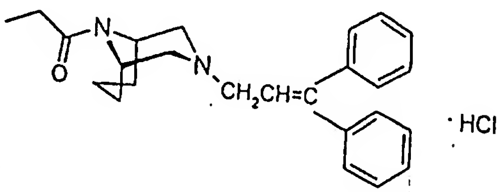
Ex.	R	Yield %	m.p. °C	Formula (Analysis[b])	IR[c] ν cm^{-1}	^{1}H-NMR δ ppm
8	H	36	oil	$C_{19}H_{26}N_2O$ (C,H,N)	1525, 1635	1.19 (t, 3H); 1.46-1.66 (m, 2H); 1.72-2.20 (m, 4H); 2.21-2.40 (m, 2H); 2.92 (br s, 2H); 3.18 (dd, 1H); 3.50-3.80 (m, 4H); 4.40 (d, 1H); 6.20-6.30 (dt, 1H); 6.60 (d, 1H); 7.20-7.40 (m, 5H).
9	4'-NO_2	22	oil	$C_{19}H_{25}N_3O_3$ (C,H,N)	1360, 1515 1630	1.19 (t, 3H); 1.47-1.70 (m, 2H); 1.72-2.20 (m, 4H); 2.21-2.40 (m, 2H); 3.01 (br s, 2H); 3.50-3.70 (m, 5H); 4.37 (d, 1H); 6.30-6.40 (dt, 1H); 6.60 (d, 1H); 7.50 (d, 1H); 8.20 (d, 2H).
10	3'-Cl	27	oil	$C_{19}H_{25}ClN_2O$ (C,H,N)	1630	1.17 (t, 3H); 1.40-1.60 (m, 2H); 1.70-2.20 (m, 4H); 2.30-2.50 (m, 2H); 2.98 (br s, 2H); 3.10 (dd, 1H); 3.40-3.60 (m, 4H); 4.40 (d, 1H); 6.20-6.40 (dt, 1H); 6.45 (d, 1H); 7.01-7.40 (m, 4H).
11	3',4'-Cl_2	36	oil	$C_{19}H_{24}Cl_2N_2O$ (C,H,N)	1635	1.17 (t, 3H); 1.40-1.60 (m, 2H); 1.70-2.10 (m, 4H); 2.20-2.40 (m, 2H); 2.89 (br s, 2H); 3.40-3.60 (m, 5H); 4.20 (d, 1H); 6.20-6.30 (dt, 1H); 6.40 (d, 1H); 7.10-7.20 (m, 1H); 7.30-7.50 (m, 2H).
12	3'-NO_2, 4'-Cl	60	oil	$C_{19}H_{24}ClN_3O_3$ (C,H,N)	1330, 1520 1630	1.19 (t, 3H); 1.42-1.62 (m, 2H); 1.70-2.20 (m, 4H); 2.20-2.40 (m, 2H); 2.92 (br s, 2H); 3.15 (dd, 1H); 3.40-3.60 (m, 4H); 4.40 (d, 1H); 6.20-6.40 (dt, 1H); 6.52 (d, 1H); 7.40-7.60 (m, 2H); 7.80 (s, 1H).
13	2'-NO_2, 5'-Cl	25	130 (dec)[a]	$C_{19}H_{24}ClN_3O_3 \cdot HCl$ (C,H,N)	1340, 1520 1635	1.17 (t, 3H); 1.42-1.65 (m, 2H); 1.70-2.20 (m, 4H); 2.37 (q, 2H); 2.93 (br s, 2H); 3.12 (dd, 1H); 3.50-3.75 (m, 4H); 4.40 (d, 1H); 6.15-6.30 (dt, 1H); 7.01 (d, 1H); 7.30 (dd, 1H); 7.56 (d, 1H); 7.92 (d, 1H).
14	2'-Cl, 5'-NO_2	30	245[a]	$C_{19}H_{24}ClN_3O_3 \cdot HCl$ (C,H,N)	1340, 1520 1560, 1635	1.17 (t, 3H); 1.48-1.68 (m, 2H); 1.72-2.18 (m, 4H); 2.34 (dq, 2H); 2.93 (br s, 2H); 3.15 (dd, 1H); 3.42-3.78 (m, 4H); 4.40 (d, 1H); 6.30-6.50 (dt, 1H); 7.01 (d, 1H); 7.65 (d, 1H); 8.05 (dd, 1H); 8.42 (d, 1H).



Ex.	R	Yield %	m.p. °C	Formula (Analysis[b])	IR[c] ν cm^{-1}	^{1}H-NMR δ ppm
1	H	72	oil	$C_{19}H_{26}N_2O$ (C,H,N)	1635	1.16 (t, 3H); 1.40-1.60 (m, 1H); 1.70-1.95 (m, 4H); 2.20-2.40 (m, 4H); 2.70-3.15 (m, 5H); 3.88 (br s, 1H); 4.70 (br, s, 1H); 6.20-6.40 (dt, 1H); 6.50 (d, 1H); 7.20-7.40 (m, 5H).
2	4'-NO_2	34	oil	$C_{19}H_{25}N_3O_3$ (C,H,N)	1350-1510 1620	1.17 (t, 3H); 1.50-1.70 (m, 1H); 1.70-1.92 (m, 4H); 2.20-2.40 (m, 4H); 2.65-3.20 (m, 5H); 3.95 (br s, 1H); 4.73 (br, s, 1H); 6.40-6.60 (m, 2H); 7.55 (d, 2H); 8.20 (d, 2H).
3	3'-Cl	64	oil	$C_{19}H_{25}ClN_2O$ (C,H,N)	1640	1.18 (t, 3H); 1.40-1.60 (m, 1H); 1.70-1.93 (m, 4H); 2.20-2.40 (m, 4H); 2.80-3.10 (m, 5H); 3.88 (br s, 1H); 4.68 (br, s, 1H); 6.10-6.30 (dt, 1H); 6.50 (d, 1H); 7.20-7.30 (m, 4H).
4	3'4'-Cl_2	72	oil	$C_{19}H_{24}Cl_2N_2O$ (C,H,N)	1635	1.11 (t, 3H); 1.42-1.63 (m, 1H); 1.70-1.90 (m, 4H); 2.20-2.40 (m, 4H); 2.80-3.10 (m, 5H); 4.05 (br s, 1H); 4.65 (br, s, 1H); 6.10-6.30 (dt, 1H); 6.40 (d, 1H); 7.10-7.50 (m, 3H).
5	3'-NO_2, 4'-Cl	76	oil	$C_{19}H_{24}ClN_3O_3$ (C,H,N)	1335, 1524 1630	1.15 (t, 3H); 1.50-1.70 (m, 1H); 1.75-1.95 (m, 4H); 2.22-2.42 (m, 4H); 2.85-3.25 (m, 5H); 3.89 (br s, 1H); 4.73 (br, s, 1H); 6.15-6.24 (dt, 1H); 6.40-6.50 (m, 2H); 7.40 (br s, 2H); 7.80 (s, 1H).
6	2'-NO_2, 5'-Cl	25	130-134[a]	$C_{19}H_{24}ClN_3O_3$·HC (C,H,N)	1340, 1520 1630	1.17 (t, 3H); 1.50-1.70 (m, 1H); 1.70-1.95 (m, 4H); 2.23-2.45 (m, 4H); 2.65-3.20 (m, 5H); 3.90 (br s, 1H); 4.72 (br, s, 1H); 6.17-6.24 (dt, 1H); 7.05 (d, 1H); 7.30 (dd, 1H); 7.56 (d, 1H); 7.92 (d, 1H).
7	2'-Cl, 5'-NO_2	31	208-210[a]	$C_{19}H_{24}ClN_3O_3$·HC (C,H,N)	1345, 1525 1640	1.17 (t, 3H); 1.50-1.70 (m, 1H); 1.70-1.95 (m, 4H); 2.25-2.45 (m, 4H); 2.80-3.20 (m, 5H); 3.95 (br s, 1H); 4.72 (br, s, 1H); 6.34-6.48 (dt, 1H); 6.95 (d, 1H); 7.53 (d, 1H); 8.03 (dd, 1H); 8.40 (d, 1H).



Ex.	R	Yield %	m.p. °C	Formula (Analysis[b])	IR[c] ν cm^{-1}	^{1}H-NMR δ ppm
15		54	102-105[a]	$C_{25}H_{30}N_2 \cdot HCl$ (C,H,N)	1650	1.17 (t, 3H); 1.40-1.60 (m, 2H); 1.70-2.10 (m, 4H); 2.20-2.40 (m, 2H); 2.89 (br s, 2H); 3.40-3.60 (m, 4H); 4.26 (d, 2H); 6.18 (t, 1H); 7.00-7.50 (m, 10H).



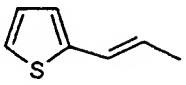
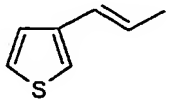
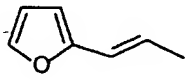
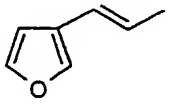
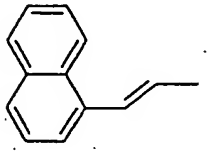
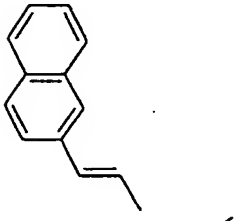
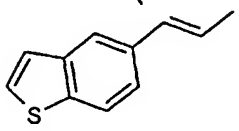
Ex.	Yield %	m.p. °C
16	59	55-57

General procedure

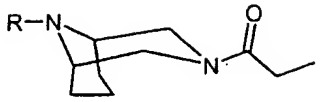
A mixture of compounds (IVa) or (IVb) (2.30 mmol), the desired cinnamyl halide (2.30 mmol) and K_2CO_3 (2.30 mmol) in acetone or butanone (13.5 ml) was refluxed for 4-12 hours. Inorganic salts were filtered off, the filtrate was evaporated and the oily residue was purified by flash chromatography (eluent CH_2Cl_3: acetone /9:1) to give the compounds reported in the following tables as oils or as hydrochlorides.

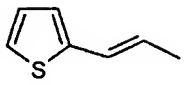
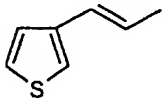
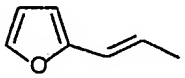
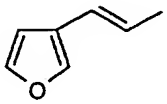
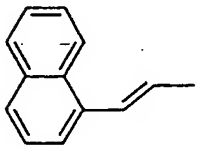
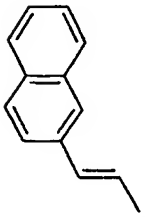
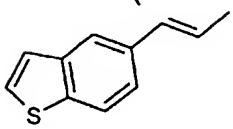
Examples 17-30

According to similar procedures, the following compounds were prepared:

Ex.	R	m.p.
17		110°
18		141°
19		125-30°
20		130-5°
21		oil
22		oil
23		153°

5



Ex.	R	m.p.
24		138°
25		143°
26		128-32°
27		134-38°
28		oil
29		oil
30		123-6°

Example 31

Pharmacological activity

Binding studies on the opioid receptors were carried out on mouse brain homogenates, in the presence of [^{3}H]-DAMGO for μ [^{3}H]-DELTORPHINE (II) for δ. [^{3}H]-U69, 593 was used on guinea pigs homogenates to evaluate the κ binding. Morphine was used as the reference compound.

The results are reported in the following tables.

Table 1

Binding affinity to μ , δ and κ receptors

Compound of Ex.	Binding affinities (Ki nM)[a]		
	μ	δ	κ
1	29±2.0	12000±1152	>50000
8	13±1.5	1750±144	2000±180

[a]Each value is the mean ± SEM of independent tests, each of them carried out in triplicate (n=3).

Table 2

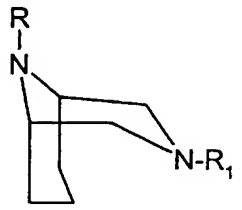
Inhibition constants towards μ opioid receptors

Compound of Ex.	[^{3}H]-DAMGO (Ki nM)[a]
2	29.0
3	70.0
4	48.33
8	13.0
9	7.66
10	8.66
11	5.83
12	18.0
13	6.0
14	6.0

[a]Values of Ki were calculated based on K_d values of 1nM for [^{3}H]-DAMGO. Values are the mean from two experiments.

CLAIMS

1. Compounds of formula 1:



(I)

wherein

R and R_1, which are different from each other, are a straight or branched C_2-C_8 acyl group;

a group of formula

$$-CH_2-CH=C(R_2)-B \quad \text{or} \quad -CH_2-CH_2-CH(R_2)-B$$

wherein:

B is a C_6-C_{10} aryl group, optionally substituted at the ortho-, meta- or para-positions with one or more substituents, which are the same or different, selected from the group consisting of C_1-C_3 alkoxy, C_1-C_2 halo alkyl, C_1-C_3 alkyl, halogens, carboxy, cyano, nitro, $CONHR_3$; a C_5-C_7 cycloalkyl group, a 5 or 6 membered heterocyclic aromatic group, optionally benzofused, having at least one heteroatom selected from nitrogen, oxygen, sulfur; said heterocyclic group optionally having one or more substituents as described above for the aryl group;

R_2 is hydrogen, C_1-C_4 alkyl, C_5-C_7 cycloalkyl or a phenyl group optionally substituted as indicated above;

and the pharmaceutically acceptable salts thereof.

2. Compounds as claimed in claim 1 wherein R or R_1 are an acyl group as

defined in claim 1 or a group of formula

$$-CH_2-CH=\underset{\displaystyle R_2}{\overset{|}{C}}-B \quad \text{or} \quad -CH_2-CH_2-\underset{\displaystyle R_2}{\overset{|}{CH}}-B$$

and B is an optionally substituted phenyl group as defined in claim 1, or a naphthyl group or a benzofused heterocyclic group.

3. Compounds as claimed in claim 1 wherein R_1 is an acyl group as defined in claim 1 and R is the group of formula $-CH_2-CH=\underset{\displaystyle R_2}{\overset{|}{C}}-B$

4. Compounds as claimed in claims 1-3 as central analgesic agents.

5. The use of the compounds of claims 1-3 for the preparation of analgesic medicaments.

INTERNATIONAL SEARCH REPORT

ıtional Application No
PCT/EP 01/01541

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/08 A61K31/4995 A61P25/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	PINNA, G. A. ET AL: "Synthesis, modeling, and m-opioid receptor affinity of N-3(9)-arylpropenyl-N-9(3)-propionyl-3,9-diazabicyclo'3.3.1!nonanes" IL FARMACO, vol. 55, no. 8, 2000, pages 553-562, XP001000530 The whole document; in particular compounds 1a-g and 2a-g. ---	1-5
Y	US-5 672-601 A (CIGNARELLA GIORGIO) 30 September 1997 (1997-09-30) cited in the application Claims 1-2; column 2, lines 44-48. --- -/--	1-5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 June 2001	22/06/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Weisbrod, T

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ıtional Application No
PCT/EP 01/01541

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	BARLOCCO, D. ET AL.: "Synthesis and mu-opioid receptor affinity pf a new series of nitro substituted 3,8-diazabicyclo(3.2.1)octane derivatives" IL FARMACO, vol. 53, 1998, pages 557-562, XP001000529 Abstract; compounds 1a-j and 2a-i. ---	1-5
Y	BALLABIO M ET AL: "2,2,6- and 2,3,5-Trimethylpiperazines as Monocyclic Analogues of the mu-Opioid Agonist 3,8-Diazabicyclo‘3.2.1!octanes: Synthesis, Modeling, and Activity" TETRAHEDRON, vol. 53, no. 4, 27 January 1997 (1997-01-27), pages 1481-1490, XP004105235 ISSN: 0040-4020 Page 1481. ---	1-5
Y	BARLOCCO, D. ET AL.: "Computer-aided structure-affinity relationship ..." J. COMPUTER-AIDEDMOLECULAR DESIGN, vol. 7, 1993, pages 557-571, XP001000932 The whole document; in particular pages 561, 571, and figures 5 and 6. ---	1-5
A	CIGNARELLA, G. ET AL.: "Trasposizione intramoleculare acilica nella serie del 3,9-diazabiciclo(3.3.1)nonano" GAZZ. CHIM. ITAL., vol. 93, 1963, pages 320-325, XP001000561 Compounds III-IX. -----	1-5

INTERNATIONAL SEARCH REPORT

Information on patent family members

tional Application No
PCT/EP 01/01541

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5672601 A	30-09-1997	IT 1274018 B	14-07-1997
		AU 1808595 A	11-09-1995
		EP 0746560 A	11-12-1996
		WO 9523152 A	31-08-1995